--52.(New) The transformed host cell of claim 47, wherein the vector encoding light chains is designated CD4-kLC-pRcCMV having ATCC No. 75194.--

--53.(New) The transformed host cell of claim 47, wherein the vector encoding heavy chains is designated CD4-IgG2HC-pRcCMV having ATCC No. 75193 and the vector encoding light chains is designated CD4-kLC-pRcCMV having ATCC No. 75194.--

--54.(New) The transformed host cell of claim 47, wherein the DNA sequence encoding heavy chains has the DNA sequence set forth in Figure 4.--

--55.(New) The transformed host cell of claim 47, wherein the DNA sequence encoding light chains has the DNA sequence set forth in Figure 5.--

REMARKS

Claims 30-35 and 44-46, which are directed to a CD4-gamma2 chimeric heavy chain homodimer, were pending in the subject application. Applicants have herein canceled these claims without disclaimer or prejudice to their right to pursue the subject matter thereof in a later filed application and added instead new claims 47-58 directed to a transformed host cell comprising at least two vectors for encoding, respectively, the heavy and the light chains of a CD4-IgG2 chimeric heterotetramer. Support for these new claims is found inter alia, in the specification as follows. Claim 47 is supported by page 12, lines 9-12; page 27, line 25 through page 28, line 24; and page 29, line 5 through page 30, line 6; Claims 48-49 are supported by page 21, lines 8-19. Claim 50 is supported by page 17,

line 21 though page 18, line 4; page 45, lines 8-13; and Figure 12; Claims 51-53 are supported by page 19, lines 1-12; and page 27, lines 4-17; Claim 54 is supported by page 14, lines 29-34; and Figure 4; and Claim 55 is supported by page 15, lines 2-8 and Figure 5. Accordingly, new claims 47-55 do not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that new claims 47-55 reciting the transformed host cell comprising vectors encoding the heavy and light chains of the CD4-IgG2 chimeric heterotetramer will be pending in the application.

In the December 3, 2001 Office Action the Examiner stated that claims 30-35 and 44-46 were rejected under 35 U.S.C. §103 (a) as being unpatentable over Capon, U.S. Patent No. 5,565,335, "for the reasons of record in the former Office Action, mailed March 9, 2001 (Paper #32) and in the Office Action of August 7, 1997 (Paper #20)". The bases for the rejection, as set forth in the subject Office Actions, are reiterated below for the sake of clarity.

Bases of Examiner's §103(a) Rejection Over Capon, U.S. Patent No. 5,565,335 In August 7, 1997 Office Action (Paper #20)

In the August 7, 1997 Office Action the Examiner stated that claims 30-35 were rejected (under 35 U.S.C. §103(a)) over Capon et al. U.S. Patent No. 5,565,335 (referred to in the Office Action as "'335"), for the reasons of record set forth in Paper No. 16, i.e., the Office Action dated November 13, 1996, at pps. 3-5.

In the subject November 13, 1996 Office Action the Examiner stated

that '335 discloses immunoglobulin fusion proteins comprising CD4 and the C-terminal Fc portion of an antibody, which Fc region consists of the hinge, CH2 and CH3 domains of the heavy chain of an IgG and which contains the intermolecular disulfide bond region of the hinge domain (col. 7, lines 50-64, and col. 26, line 44 to col. 28, line 14). The Examiner further stated that '335 also discloses that CD4 fused to the constant domain of an IgG heavy chain results in secretion of a CD4-IgG homodimer. The Examiner also stated that '335 also teaches a CD4-IgG heterotetramer composed of two CD4-light chain fusion proteins and two CD4-heavy chain fusions (col.6, line 61 to col.7, line 11) and discloses that suitable fusion proteins can be obtained from IgG-1,-2,-3 or -4, as well as IgA, IgE, IgD or IgM (col. 7, lines 47-49). The Examiner then went on to state that '335 further teaches that CD4-IgG fusion proteins can be conjugated to toxins such as deglycosylated ricin A chain or Diptheria toxin (col.8, line 62 to col.9, line 7), and that '335 discloses that CD4-IgG fusion proteins can be used in compositions to treat HIV (col.1, lines 11-15) or can be labeled for use as a diagnostic reagent (col. 10, line 66 to col. 11, line 4). The Examiner also stated that although '335 does not exemplify a CD4-IgG fusion protein, it would have been obvious to one having ordinary skill in the art at the time the invention was made to follow the teachings and motivations of '335 to make any CD4-IgG homodimer, including the CD4-IgG homodimers recited in applicants' then pending claims, or heterotetramers, as well as conjugates thereof. The Examiner continued by stating that the skilled artisan would have had a reasonable expectation of success that a CD4-IgG2 homodimer would be biologically active because the constant domains of IgG proteins are similar to one another and because '335 teaches that any IgG

subtype can be used in the CD4-IgG fusion. The Examiner also stated that the CD4-IgG2 homodimers would be less likely to increase infection of monocytes/macrophages by HIV than CD4-IgG1 when administered *in vivo*, and that the specification provides no *in vivo* or *in vitro* evidence that CD4-IgG2 has these properties. The Examiner therefor stated that the change of IgG1 in the CD4-IgG fusion to IgG2 is considered *prima facie* obvious since a minor change in the chemical configuration of a molecule is considered to be *de minimus*, and is not deemed to impart any patentable differences, absent evidence to the contrary.

Returning now to the August 7, 1997 Office Action, the Examiner stated therein that the "newly added" claims (i.e., nos. 44-46) were rejected over '335 because '335 also teaches an expression vector comprising DNA encoding CD4-IgG (col.11, lines 16-30 and col.12, line 49 to col.13, line 10), a method of producing CD4-IgG (col. 14, lines 29-42), and a method of producing CD4-IgG in CHO cells (col.12, lines 65-66). The Examiner stated that it would therefore have been obvious to one having ordinary skill in the art at the time the invention was made to follow the teachings and motivations of '335 to make any CD4-IgG homodimer, including the CD4-IgG2 homodimer recited in the then pending claims, using an expression vector comprising DNA encoding CD4-IgG2, and to use host cells comprising this expression vector to produce CD4-IgG2 in CHO cells, as suggested by '335.

The Examiner additionally stated that applicants' arguments filed May 19, 1997 were fully considered but were not persuasive. The Examiner stated that applicants argued that there is no close

structural similarity between the CD4-IgG1 exemplified by '335 and the CD4-IgG2 taught by applicant, nor that any of the molecules taught by Capon exhibit sufficient close structural similarity to the then-claimed compositions. The Examiner further stated that applicants also asserted that Capon does not teach or suggest applicants' polypeptide. The Examiner stated that both the CD4-IgG2 and the CD4-IgG1 taught by Capon appear to have identical CD4 extracellular domains comprising the N-terminus domain of the homodimer, and differ only in that the C-terminus domain of the homodimer is IgG1, in the case of Capon, or IgG2, in the instant case. The Examiner went on to state that it was well-known in the art at the time the invention was made that the constant domains of IgG1 and IgG2 are both structurally and functionally related to one another, and have a sequence identity of about 95% (see 5,431,793, col.7, lines 42-44).

The Examiner further stated that applicants had asserted that the disclosure of Capon of a method for producing the CD4-IgG2 is not a proper basis for determining whether the compound recited in the then pending claims is obvious. The Examiner stated that this argument was unpersuasive because Capon's method was not the basis of obviousness. The Examiner stated that Capon's express teaching that suitable fusion proteins are obtained from IgG2 is the basis. The Examiner stated that this teaching was pointed to in the rejection set forth in Paper No. 16, page 4, lines 3-5. The Examiner stated that it is the composition itself that is suggested by Capon. The Examiner stated that Capon discloses a motivation for producing the claimed fusion protein (col.1, lines 11-15 and col.10, line 66 to col.11, line 4; also see discussion in Paper No.

16, page 4) and also provides a method for producing the CD4-IgG2 DNA, vectors, host cells, method of producing the protein recombinantly and the protein itself. The Examiner stated that Capon provides not only a teaching for the composition CD4-IgG2, but also a method for producing the claimed compound and a reasonable expectation of success since Capon exemplifies CD4-IgG1, a highly structurally and functionally similar compound.

The Examiner stated that applicants urged that there is no reasonable expectation of success in obtaining a functional CD4-IgG2 because of the amino acid differences between CD4-IgG1 and CD4-IgG2, but that, as discussed above, since IgG and IgG2 are virtually identical in their constant domains, one having ordinary skill in the art would have the reasonable expectation that one could substitute the constant domain of IgG2 for that of IgG1 in the molecule taught by Capon and retain the functional properties of the fusion protein, especially since Capon specifically teaches that the constant domain of any IgG isotype could be used. The Examiner further stated that there is no requirement under 35 U.S.C. §103 that there be absolute predictability of success, but rather only a reasonable expectation of success in producing an obvious variant of a known compound.

The Examiner went on to state that applicants had argued that there is no motivation to make the specific amino acid alterations between CD4-IgG1 and CD4-IgG2 but that this argument is unpersuasive because the only differences in amino acid sequence between CD4-IgG1 and CD4-IgG2 are those amino acid residues which differ between the constant domains of IgG1 and that of IgG2. The

Examiner stated that since Capon suggests a CD4-IgG2 fusion protein, those minor amino acid sequence differences between CD4-IgG1 and CD4-IgG2 were known by Capon or by anyone having ordinary skill in the art. The Examiner therefore stated that one having ordinary skill in the art following the teachings of Capon would have produced a CD4-IgG2 with the same specific amino acid alterations as recited in the then pending claims.

Bases of 35 U.S.C. §103(a) Rejection Over Capon, U.S. Patent No. 5,565,335 In March 9, 2001 Office Action (Paper #32)

In the March 9, 2001 Office Action the Examiner stated that applicants' arguments traversing the §103 rejection over Capon U.S.P. 5,565,335 had been considered but had not been found persuasive for the reasons of record and for the reasons which follow.

The Examiner stated that applicants had argued the criticality of the specific amino acid composition and structure of the CD4 portion and of the IG portion of their chimera, and that Capon teaches away from the claimed construct. The Examiner stated, however, that this is not persuasive because, while Capon's preferred embodiment does not have the exact structure claimed by applicants, the Capon reference was not applied in order to anticipate the claims, but had been applied to render the claims obvious, and Capon clearly (1) envisions making chimeras using modified CD4 and immunoglobulin chains (see for example col.5, lines 26-32), (2)teaches a CD4-IgG2 fusion protein (col. 7, lines 47-49) and (3)does not teach away from the claimed invention.

The Examiner further stated that applicants had argued that their

construct has unexpected properties, with reference to Exhibits 1 and 2 submitted with their First Submission Under 37 C.F.R. §1.129 (a) dated June 8, 1999, but that this argument cannot be considered, absent evidence being properly presented. The Examiner stated in this regard that if applicants wished to provide evidence for consideration by the Patent Office, they must provide a declaration according to Rule 1.132.

The Examiner further stated that applicants had argued that their CD4-gamma2 chimeric heavy chain homodimer construct has unexpected properties, by referring to results published by Gauduin, Journal of Virology, 70(4):2586-2592, April 1996, and Capon, Nature 337:525-531, 9 February 1989, (Exhibits 3 and 4 to the June 8, 1999 submission). The Examiner stated in response that Gaudin teaches a CD4-IgG2 construct that is more potent than sCD4 in ex-vivo neutralizing HIV-1 and Capon (Nature) teaches that sCD4 and CD4-IgG1 are equipotent in neutralization. The Examiner then stated that applicants therefore conclude that "CD4-gamma2 is more potent than CD4-gamma 1". The Examiner stated that this is not persuasive, because applicants, in the specification and in their arguments against the Capon '335 patent, insist upon the criticality of the specific amino acid composition and secondary structure of their chimera for its function. The Examiner stated that she could not clearly ascertain if the claimed CD4-gamma2 chimeric heavy chain homodimer, and "CD4-IgG2, a tetrameric human antibody prepared from a human IgG2 with replacement of each heavy-and light-chain variable region by the first and second domains of human CD4" disclosed by Gauguin, page 2586, col.2, lines 3-6, are identical in amino acid composition and structure/conformation, and therefore it was not clear to her if the activity of the claimed CD4-gamma2 chimeric heavy chain homodimer and of the cited CD4-IgG2 tetrameric antibody are identical or comparable.

Applicants' Response To The Claim Rejections Based On 35 U.S.C. §103(a)

Applicants respectfully traverse the Examiner's §103(a) rejection of claims 30-35 and 44-46 directed to the CD4-gamma 2 chimeric heavy chain homodimer over Capon U.S. Patent No. 5,565,335 and contend that the invention as recited in those claims is not obvious over the cited patent. Nevertheless, applicants, without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application, have hereinabove canceled claims 30-35 and 44-46 without prejudice or disclaimer to their right to pursue the subject matter of those claims in a later-filed application, and added new claims 47-55 directed to a transformed host cell comprising vectors comprising DNA sequences encoding heavy and light chains of a CD4-IgG2 chimeric heterotetramer, such that the CD4-IgG2 chimeric heterotetramer produced in the cell is capable of neutralizing an HIV-1-infected individual's HIV-1 virus. The support for these new claims is indicated above. Applicants contend that the invention recited in the new claims 47-55 is neither disclosed nor suggested by the subject Capon reference and thus these new claims are not obvious over the cited reference pursuant to 35 U.S.C. §103(a).

Further in support of the patentability of new claims 47-55, applicants note that in responding to applicants' argument in an earlier response that their construct has unexpected properties, the Examiner stated (see discussion at p.12 above) that such arguments could not be considered absent evidence being properly

presented, i.e., in a declaration under 37 C.F.R. §1.132. In response, the Examiner is respectfully informed that evidence (i.e., including a Declaration Under 37 C.F.R. §1.132 of Dr. Paul J. Maddon, a co-inventor of the present invention) of such unexpected properties for applicants' chimeric heterotetramer (which is produced by the presently claimed transformed host cell) has been presented, however, in two responses filed, respectively, February 26, 2001 and November 15, 2001 in a related application (i.e., application Serial No. 08/484,681 filed June 7, 1995 and examined by Examiner P. Gambel in Art Unit 1644) which claims the subject chimeric heterotetramer. That evidence is being reiterated herein in support of the patentability of the present claims. Although the present claims are directed to a transformed host cell and not to the chimeric heterotetramer, per se, applicants submit that, as recited, e.g., in claim 47, the subject host cell is specifically adapted to produce the CD4-IgG2 chimeric heterotetramer for which unexpected properties are demonstrated, i.e., neutralization of an HIV-1-infected individual's HIV-1 virus, and thus evidence provided by applicants equally supports the non-obviousness of claims to the subject host cell.

Relative to the disclosure of the cited Capon '335 reference, the patentability of applicants' chimeric heterotetramer, i.e., as produced by the presently claimed transformed host cell, may be viewed either from the perspective of a species relative to a genus, or from the perspective of a species relative to the closest species disclosed. From either perspective, however, the chimeric CD4-IgG2 heterotetramer provides unexpected results. Therefore both the heterotetramer and the transformed host cell which produces the heterotetramer, are unobvious and thus patentable.

1. A genus does not render obvious a nondisclosed species within the genus having unexpected properties.

U.S. Patent No. 5,565,335 (the "Capon patent") does not specifically describe applicants' chimeric CD4-IgG2 heterotetramer, nor does it describe the presently claimed transformed host cell adapted for producing the subject heterotetramer. The Capon patent may be viewed as a disclosure of a genus which includes CD4-Ig tetramers and CD4-Ig dimers wherein the Ig portions of such tetramers or dimers may be IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgD, or IgM and the CD4 portions may be V1, V2, V3, V4, V1V2 or V1V2V3V4.

The Capon patent discloses at column 7, lines 47-49 that IgG1 is preferred. The disclosure of a chemical genus does not necessarily render obvious any species that happens to fall within it. See In re Jones, 21 USPQ 2d 1941 (CAFC 1992). The genus described in the Capon patent does not render obvious applicants' heterotetramer, i.e., the species of a CD4-Ig tetramer wherein (i) the Ig portion is IgG2, and (ii) the CD4 portion is V1V2, because applicants' species provides unexpected results relative to other species within the genus. That is, previously known CD4-Ig molecules are not effective for neutralizing HIV, as described below. It was unexpected that applicants' CD4-IgG2 tetramer having both V1 and V2, would be effective for neutralizing an HIV-1 infected individual's HIV-1 virus. It is therefore submitted that, as applicants' species of tetramer is unobvious, so also is the transformed host cell adapted for forming the subject tetramer species.

a. The Capon CD4-Ig dimer

The Capon CD4-Ig dimer, constructed as described in the Capon

patent ("Capon CD4-Ig dimer") is not effective for neutralizing an HIV-1-infected individual's HIV-1 virus. In support, applicants attach hereto as **Exhibit A** Hodges et al. (1991) Antimicrobial Agents and Chemotherapy 35:2580-2586. This paper presents results of an in vivo study using Capon's CD4-Ig **dimer**. Page 2580 states that treatment with this dimer did not result in significant changes in CD4 lymphocyte counts or p24 antigen levels in serum. Page 2584 of the reference teaches that although some individual patients had persistent decreases in HIV antigen levels in serum, overall consistent changes in HIV antigen levels and numbers of CD4 lymphocytes were not observed during the initial phase of study. In fact, page 2583 recites that **"significant sustained changes in HIV antigen levels in serum were not seen overall."** [emphasis added] Table 2 demonstrates the data that changes in total lymphocyte, CD4, and CD8 were not noted.

In further support, applicants attach hereto as **Exhibit B** Collier et al (1995) Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 10:150-156. This paper also demonstrates results of an in vivo study using the Capon CD4-Ig **dimer**. Page 150 recites that the dimer showed little antiviral activity. Page 153 recites that all 17 subjects who had detectable HIV p24 antigen remained positive, with no significant changes in titer. Page 154 characterized the in vivo antiviral effects of the dimer as **unimpressive**. [emphasis added]. Page 155 recites that the dimer had a lack of effect on the virologic and immunologic parameters of the study.

Accordingly, the Capon CD4-Ig dimer is not effective for neutralizing an HIV-1-infected individual's HIV-1 virus.

The CD4-IgG **dimer** disclosed by applicants also does not

significantly neutralize HIV-1 in an HIV-1 infected subject. Evidence in support of this assertion may be found at pp. 62-63 of applicants' related application Serial No. 08/484,681 wherein, as noted above, the evidence in support of the patentability of applicants' CD4-IgG2 chimeric heterotetramer was originally submitted. The subject '681 application describes results of an in vitro study of the ability of the dimer (i.e. CD4-gamma 2) to neutralize HIV-1. The data show that the IC_{50} value in ug/ml was 7.7 fold higher for the dimer than for the tetramer (wherein the IC_{50} value is the concentration needed to give 50% neutralization). Accordingly, the dimer did not significantly neutralize HIV-1 in vitro as compared to the tetramer.

c. The CD4-IgG tetramer which can be produced by the presently claimed transformed host cell

Accordingly, certain members of the genus (i.e. the Capon dimer and the dimer disclosed in the subject application) were not effective for neutralizing HIV-1. In contrast, however applicants' CD4-IgG2 tetramer containing both V1V2, i.e., as may be produced by the presently claimed transformed host cell, is effective for neutralizing an HIV-1-infected individual's HIV-1 virus.

In support, applicants attach hereto as **Exhibit C** a paper entitled "Single-Dose Safety, Pharmacology and Antiviral Activity of the Human Immunodeficiency Virus (HIV) Type I Entry Inhibitor PRO 542 in HIV-Infected Adults" Jacobson et al. Journal of Infectious Diseases, vol 182:326-329 (2000) which demonstrates the in vivo efficacy of applicants' CD4-IgG tetramer to inhibit human immunodeficiency virus infection of a CD4+ cell. Applicants' CD4-IgG2 tetramer, which may be produced, e.g., by means of the presently claimed transformed host cell, is also referred to as PRO 542. The data corroborates that infusion of applicants' CD4-

IgG2 tetramer into an adult subject provides in vivo antiviral activity. Page 6 of this paper describes that a significant decline in plasma HIV RNA was observed following a single dose of 10 mg/kg of applicants' CD4-IgG2 tetramer. Page 6 also discloses that viral load reductions were observed in the majority of patients at all times post-treatment. Page 9 recites that "measurable reductions in both plasma HIV RNA and plasma viremia were observed following treatment with single-dose of the tetramer, indicating that the compound possesses antiviral activity in humans."

In further support of the in vivo efficacy of applicants' tetramer i.e., as produced by the claimed transformed host cell, applicants attach hereto as **Exhibit D** a paper entitled "Recombinant CD4-IgG2 in Human Immunodeficiency Virus Type 1-Infected Children: Phase 1 /2 Study" by William Shearer et al, The Journal of Infectious Diseases (2000) 182:1774-1779. This paper shows in figure 2 that treatment of HIV-1 infected children with applicants' tetramer resulted in reductions in both HIV RNA and infectious units per million (IUPM) cells. As described on page 1778, the treatment appeared to produce acute, sometimes sustained decreases in serum HIV-1 RNA concentrations and cellular IUPM in individual pediatric patients.

Accordingly, certain molecules known as of October 2, 1987 (i.e., the earliest date of which priority is claimed in the Capon patent) within the genus of CD4-Ig molecules, such as Capon's CD4-Ig dimer, and certain unknown molecules such as applicants' CD4-Ig dimer, are not capable of neutralizing HIV-1 in an HIV-1 infected subject. Thus, it was unexpected that applicants' CD4-Ig tetramer produced, e.g., by the claimed transformed host cell, which includes V1V2 would neutralize an HIV-1-infected individual's HIV-1 virus.

2. A species does not render obvious another species which has

unexpected properties.

Alternatively, the species in the Capon patent which can be considered closest to applicants' CD4-IgG2 chimeric heterotetramer, i.e., as may be produced by the presently claimed transformed host cell, is that described in Example 2 of the Capon patent which purports to set forth a procedure for obtaining a tetramer which comprises IgG2 and only the **V1** domain of CD4. Applicants' heterotetramer is distinct from this species described in Capon because the heterotetramer produced by the transformed host cell presently claimed comprises **both V1 and V2** domains of CD4. That the subject tetramer can neutralize an HIV-1 infected individual's HIV-1 virus was unexpected relative to the lack of knowledge about the Capon tetramer purportedly capable of being made based on Example 2 of the Capon patent.[1]

The Capon patent states at column 1, lines 13-15, that the compositions described are useful in the treatment of HIV infection. However, not only is the Capon **dimer** not effective in neutralizing an HIV-1-infected individual's HIV-1 virus in vivo (as described above), the Capon **tetramer** also does not neutralize an HIV-1-infected individual's virus. In fact, the Capon tetramer cannot be made, as evidenced in Dr. Maddon's declaration **(Exhibit**

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[1] Researchers at Progenics Pharmaceuticals Inc. tried to make a CD4-IgG tetramer having only the V1 domain of CD4. However, their experiments demonstrate that a heterotetramer having only the V1 domain of CD4 does not secrete when expressed in a competent cell [see Declaration under 37 C.F.R. 1.132 of Paul J. Maddon originally attached as Exhibit C to the response filed on February 26, 2001 in application Serial No. 08/484,681, a copy of which (together with its Exhibits 1-11) is provided herewith as **Exhibit E**]. Accordingly, a CD4-IgG tetramer having only the V1 domain of CD4, such as the Capon tetramer, cannot be made.

E).

Since a CD4-Ig tetramer having only the V1 domain of CD4 is unable to be secreted and unable to neutralize HIV-1, it was unexpected that **applicants'** CD4-IgG tetramer which includes both the V1 and V2 domains of CD4 would neutralize an HIV-1 infected individual's HIV-1 virus.

Prior to the present invention, the prior art taught that the **V1** domain of CD4 is analogous to a complementarity-determining region (CDR) of an antibody **variable** region, while the **V2** domain resembles a **constant** domain. See last paragraph of introduction of Ryu et al. (1990) Nature 348:419-426, attached hereto as **Exhibit F**. Applicants point out that the terminology D1D2 and V1V2 are used interchangeably when referring to CD4 domains. In the chimeric-antibody prior art, it was taught that the antigen binding variable region (devoid of the constant region) of a particular antibody could be "grafted" onto a different constant region framework of an immunoglobulin molecule (devoid of the variable region), retaining the function of the antigen binding variable region. Since the prior art taught that the V1 domain of the CD4 resembled a CDR of an antibody variable region and the V2 domain of CD4 resembled a constant domain of an immunoglobulin molecule, one skilled in the art would have been lead to using only V1 of the CD4, devoid of the V2 constant domain of CD4, to graft onto a different constant region framework. Therefore, it would have been expected by those skilled in the art that addition of the V1 domain would be sufficient to make a functional secretable CD4-IgG tetramer because V1 is analogous to a CDR variable domain. However, as described herein, a CD4-IgG tetramer having only the V1 domain of CD4 does not secrete and as such, has no function. Accordingly, it was unexpected that inclusion of the V2 domain (which resembles a

constant domain) in addition to the V1 domain of CD4 would provide results which differ from the inclusion of only the V1 domain, i.e. secretion of a functional CD4-Ig tetramer. Accordingly, it was also unexpected that inclusion of such a constant-like V2 region in addition to the V1 region would result in CD4-IgG tetramer capable of neutralizing an HIV-1 infected individual's HIV-1 virus.

Moreover, even if one were to assume that the Capon tetramer does secrete and neutralize an HIV-1-infected individual's HIV-1 virus (which it does not), it would have been unpredictable to one skilled in the art as to the effect the addition of the constant-like V2 domain would have had on the Capon's tetramer activity. The resultant V1 variable region-like domain of CD4 plus the V2 constant region-like domain of CD4 plus the constant region of a human IgG molecule, would not have been analogous to a chimeric antibody of the prior art and moreover, the overall size of the resultant tetramer would be much larger than the Capon tetramer. Thus, one skilled in the art would have concluded that the addition of the V2 constant region-like domain of CD4 would have abrogated any HIV-1 neutralizing activity of Capon's tetramer.

Conclusion

Viewed in either way (i.e. the genus-species comparison or the species-species comparison), applicants' CD4-IgG2 chimeric heterotetramer provides an unexpected result relative to the teachings of the cited references because the subject heterotetramer is able to neutralize an HIV-1 infected individual's HIV-1 virus. Applicants further submit that the presently claimed transformed host cell is also unobvious over the prior art Capon '335 reference, as the subject host cell is particularly adapted to encode the heavy and light chains of, and thus to produce, the unobvious CD4-IgG2 chimeric heterotetramer. Accordingly, the cited reference also does not render applicants' presently claimed

invention obvious.

Applicants thus submit that the cancellation of the pending claims with the addition of new claims 47-55 obviates the §103 rejection of claims 30-35 and 44-46. They respectfully request that the Examiner reconsider and withdraw the rejection under §103 and earnestly solicit allowance of the now pending claims, nos. 47-55.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.

The fees believed to be due for this case include $460.00 for a three-month extension, plus $370.00 for filing this second submission after final rejection, for a total of EIGHT HUNDRED THIRTY DOLLARS ($830.00). However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, U.S. Patent and Trademark Office, Washington, D.C. 20231

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